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## Psychological interventions for treating and preventing recurrence of foot ulcers in people with diabetes (Protocol)

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# Psychological interventions for treating and preventing recurrence of foot ulcers in people with diabetes

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effects of psychological interventions on healing and prevention of recurrence of DFU.

## BACKGROUND

### Description of the condition

Diabetes mellitus (DM) refers to a group of metabolic disorders resulting from defects in insulin secretion or insulin action, or both, giving rise to chronic hyperglycaemia (elevated blood glucose levels) (ADA 2009). There are two main types of DM: Type 1 (T1DM) usually develops in childhood, or early adulthood, and is characterised by insulin deficiency as a result of auto-immune destruction of the insulin-producing beta cells; Type 2 (T2DM) develops when there is a gradual beta cell destruction and reduced insulin secretion, and/or when the insulin produced does not work effectively (insulin resistance). Over the last decade the global prevalence of DM has increased substantially in countries at all income levels, mirroring the worldwide obesity epidemic

(WHO 2016). It is anticipated that almost 600 million people worldwide will have DM by the year 2035 (IDF 2015).

Diabetic foot disease, characterised by peripheral neuropathy (loss of sensation in the feet), ischaemia (reduced blood flow to the feet) and foot ulceration, is a major complication of diabetes. Approximately 50% of people with diabetes will develop peripheral neuropathy, while 15% to 25% will develop foot ulceration during the course of the disease (Bus 2016). Diabetic foot ulceration (DFU) can be defined as a full-thickness wound below the ankle in a person with diabetes (Hoogeveen 2015), caused by peripheral neuropathy or ischaemia or both, and consequent trauma to the foot (Alexiadou 2012). Chronic ulceration can lead to adverse patient outcomes and complications including sepsis and increased foot morbidity, which may require distal (digital or transmetatarsal) or lower limb amputation (above or below knee). The progression and outcome from DFU is worsened by neuropathy and ischaemia

and a myriad of other complications of diabetes such as impaired immune function, poor tissue oxygenation and defective healing (Falanga 2005). DFU is considered the most prevalent and costly of all diabetes complications and is associated with a five-year mortality rate of 50% (Armstrong 2011).

The cost of treating DFU poses a significant economic burden. The EURODIALE study found the estimated costs associated with treatment of DFU to be EUR 10 billion per year in Europe (Schaper 2012). In the UK, DFU is estimated to account for 20% of the total cost of diabetes care (Wounds International Expert Working Group 2013). DFU also poses significant personal costs for individuals.

There is a higher risk for ulceration and re-ulceration in men (Iverson 2008). The underlying cause of this may be associated with different effects of ulceration on male behavioural, emotional, cognitive and social influences which effect healing and prevention of DFU recurrence (Vedhara 2012). Gender differences were seen in a meta-analysis of the effects of psychological interventions in cardiac patients, suggesting that gender-tailored programmes need to be developed and evaluated (Linden 2007).

Depression is common in DFU and the prevalence is double that of the non-diabetic population (Ali 2006; Anderson 2001; Pearson 2014). The evidence to date suggests a bi-directional relationship: depression is associated with increased risk of T2DM (Nouwen 2010), and the onset of diabetes is associated with subsequent depression (Mezuk 2008), poor glycaemic control (Lustman 2000) and diabetic complications (De Groot 2001). This may be attributed to the physiological stress of living with diabetes, the psychological burden of self-managing diabetes and coping with the complications of the disease. Depression substantially increases the risk of DFU in a dose response manner: the greater the depressive symptoms the greater the risk of DFU (Iverson 2015). We also know that depression is associated with a two-fold increased risk of mortality in people with their first DFU at five years (Winkley 2012). Furthermore, the health-related quality of life among patients with diabetes and foot ulcers is much lower than the general population across a wide range of domains including restrictions in daily activities, physical restrictions and lower social functioning (Ribu 2007; Winkley 2009). Twenty per cent of people with severe mental illness have diabetes, usually T2DM, and these people and people from other hard-to-reach groups, such as people with dementia or learning disabilities, are more likely to die prematurely from cardiovascular disease (Brown 2010; NHS Health Scotland 2004). They are also more likely to be at risk of suffering from the complications of diabetes such as diabetic foot disease, as they are less likely to receive adequate support with diabetes management (Mitchell 2009). However, as awareness is raised of these inequalities (Holt 2015), more complex interventions, such as psychological interventions, may be developed to support these individuals.

The development of a foot ulcer is a sign of progressive disease, and once present, DFU can prove challenging to heal (Wounds

International Expert Working Group 2013). Strategies associated with the prevention of DFU and optimal management of active DFU are key to reducing the burden of diabetic foot disease. Specialist multidisciplinary teams have been shown to reduce the incidence of ulceration and amputation (Edmonds 1986); however, despite best practice, many wounds fail to heal and the risk of recurrence of DFU remains high (Dubsky 2012). Holding certain beliefs about diabetes, such as an individual viewing themselves as having control or influence on ulceration, is associated with better engagement with self-care in DFU (Vedhara 2014), and has also been shown to have a significant effect on survival from DFU (Vedhara 2016). Healthcare practitioners such as diabetes professionals and podiatrists need the knowledge, skills and attitudes to facilitate an empowering approach and better diabetes self-management. We know that it is possible to train generalist/diabetes clinicians in psychological techniques to improve glycaemic control (Alam 2009; McGloin 2015), but it is necessary to establish the current level of evidence for the effectiveness of psychological interventions in DFU.

## Description of the intervention

Psychological interventions are by nature complex and difficult to define and precise definitions are frequently missing from intervention studies and reviews (Hodges 2011). New CONSORT guidelines are being developed to guide the reporting of psychological intervention studies but are as yet unavailable (Mayo-Wilson 2013).

Psychological interventions are those that use 'the therapeutic alliance between the patient and therapist to bring about change in emotional, cognitive and behavioural functioning' (Ismail 2004 p1589). Psychological interventions are distinct from other types of intervention such as education or medication. The aim is to improve the psychological and physical well-being of patients using a form of communication, often talking therapy, to foster a supportive relationship in order to promote patient autonomy and empowerment in the self-management of their chronic condition (Alam 2009; Kulzer 2007; McGloin 2015). A psychological intervention includes a psychotherapeutic (improved emotional, cognitive or behavioural functioning) or psychosomatic mechanism (addressing the stress of having a condition such as diabetes) (Goldbeck 2014). Psychological interventions include, for example, supportive or counselling therapy, cognitive behavioural strategies (an umbrella term for problem-solving, contract setting, goal setting, self-monitoring of behaviours and enlisting social support), psychotherapy or psychological techniques such as motivational interviewing and also newer techniques such as positive psychology and acceptance commitment therapy, both derived from cognitive behavioural therapy (CBT) (Goldbeck 2014; Ismail 2004). Despite the breadth of psychological interventions that might be used in the treatment of DFU in people with diabetes, there is no consensus on how such interventions should

be classified. Psychological treatments may be categorised in a variety of ways including current behaviour change taxonomies or according to underlying theory.

## How the intervention might work

Psychological interventions aim to reduce levels of psychological distress, including depression or perceived levels of stress of the individual, a factor that negatively effects wound healing (Ebrecht 2004; Walburn 2009). Chronic stress increases cortisol release which has an anti-inflammatory effect. This disrupts the normal functioning of immune cells required for the inflammatory phase of wound healing and therefore delays wound healing (Ebrecht 2004; Guo 2010; Kiecolt-Glaser 1995; Vileikyte 2007). Psychological interventions aim to reduce levels of stress or perceived levels of stress, and there is some evidence to suggest that they can positively impact the rate of wound healing (Weinman 2008). The response to stress can also result in unhealthy behaviours (Guo 2010). Psychological interventions may help people improve their levels of confidence in controlling their diabetes and diabetes self-management and reduce the potential for ulcer recurrence by enabling or supporting people to make lifestyle changes that promote wound healing, including adequate sleep, physical activity, limb elevation and offloading, wearing of a total contact cast and appropriate footwear, healthy nutrition, reduced alcohol intake, smoking cessation and improved social interaction (Armstrong 2005; Brown 2012; Guo 2010). Whilst psychological interventions for people with DFU may be beneficial, there may be obstacles to implementation, such as a lack of awareness of psychological issues on the part of health professionals, and this needs to be considered. For example, some health professionals may not be aware that psychological problems are more common in diabetes and that these are associated with adverse outcome. Addressing these issues may involve additional training and ultimately provide access to psychological services.

## Why it is important to do this review

A higher rate of ulcer recurrence is associated with poor glycaemic control and this may reflect poor patient engagement and a lack of psychological support (Dubsky 2012). Illness beliefs about DFU have recently been shown to be linked to survival and predict foot self-care practice in DFU (Vedhara 2014; Vedhara 2016). Psychological interventions may have the potential to improve self-care and reduce the morbidity and costs associated with DFU. There is a need for a systematic review of the evidence on the effectiveness of psychological interventions in DFU. This will allow people with DFUs, health care professionals caring for them and those trying to prevent recurrence to take informed decisions regarding their implementation.

A number of systematic reviews of psychological interventions in diabetes have been conducted or are planned (Alam 2009; Chew 2017; Ismail 2004; Steed 2003), but to our knowledge no systematic review of psychological interventions in promoting healing and preventing recurrence of DFU has been completed.

## OBJECTIVES

To evaluate the effects of psychological interventions on healing and prevention of recurrence of DFU.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include published and unpublished RCTs including quasi-randomised, cross-over and cluster RCTs. We will only include cross-over trials that report outcome data at the end of the first treatment period and prior to cross-over. We will not limit with respect to language of the report, year or place of publication.

#### Types of participants

Eligible participants will include people of 18 years or older, in any care setting, including their own home, with a DFU or a history of DFU. The diagnosis of DFU will be based on that determined by trial authors.

#### Types of interventions

For the purposes of this review, a psychological intervention will be considered for inclusion if it meets the following criteria (adapted from Goldbeck 2014 and Ismail 2004):

- tailored to the individual and includes psychological interventions with a psychotherapeutic or psychosomatic mechanism of action. This includes, but is not limited to, cognitive behavioural therapy, cognitive therapy, psychodynamic therapy, counselling (techniques of goal setting, problem solving, identifying strengths and barriers, motivational interviewing), family systems or systemic therapy, and others such as supportive, relaxation, and biofeedback;
- provided in structured interactions, face to face or via telephone in individual or group setting, between a participant and a facilitator;
- provided by facilitators who may or may not have specific qualifications or training in psychology or psychotherapy;

- interactions are of any frequency or duration;
- the main target of the psychological intervention is promoting healing and preventing recurrence of DFU.

The following broad categories will be used to classify the different types of interventions (Goldbeck 2014):

- cognitive behavioural therapy;
- cognitive therapy;
- psychodynamic therapy;
- counselling;
- family systems or systemic therapy;
- other interventions.

We will exclude studies of the following interventions:

- interventions which rely only on a structured or unstructured intervention utilising teaching or instructional approaches providing information related to DFU;
- specific interventions focused on preventing the first incidence of foot ulceration.

Where data are available, we will undertake the following comparisons:

- psychological interventions versus standard care or versus another psychological intervention or versus education on healing of DFU;
- psychological interventions versus standard care or versus another psychological intervention or versus education on recurrence of DFU.

## Types of outcome measures

### Primary outcomes

The primary outcome for this review is complete wound healing. This may be presented in either or both following formats:

- the proportion of wounds completely healed (frequency of complete healing by group);
- time to complete wound healing (survival data: study-level data reported as a hazard ratio (HR) with standard error (SE)).

Recurrence will be assessed as:

- time to recurrence (survival data: study-level data reported as an HR with SE);
- number of recurrences.

We anticipate that trials will have different follow-up times. For this review we will group the timing of follow-up data at the following time periods: short-term follow-up (up to 12 weeks following treatment); medium-term follow-up (more than 12 weeks and up to six months after the end of treatment); and long-term follow-up (longer than six months and less than 12 months after the end of treatment).

We will include non-censored data, i.e. mean or median time to healing without survival analysis, if there is an indication that all

participants experienced complete healing during the trial period but consider these as less robust assessments of these outcomes, and will not therefore include these data in preparing the 'Summary of findings' table(s).

### Secondary outcomes

- Amputations (major or minor).
- Health-related quality of life, as measured by tools such as SF-36 or EQ5D and/or disease-specific quality of life instruments designed for use with DFU patients.
- Self-efficacy as measured by tools such as the Diabetes Empowerment Scale and/or the Footcare Confidence Scale.
- Cost.

## Search methods for identification of studies

### Electronic searches

We will search the following electronic databases to identify reports of relevant studies:

- the Cochrane Wounds Specialised Register (to present);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue);
- Ovid MEDLINE (1946 to present);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, to present);
- Ovid Embase (1974 to present);
- EBSCO CINAHL Plus (1937 to present);
- Ovid PsycINFO (1806 to present).

The provisional search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL) is presented in [Appendix 1](#). We will adapt this strategy to search the other databases listed above. We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the Embase search with the Ovid Embase randomised trials filter terms developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL Plus search with the randomised trials filter terms developed by the Scottish Intercollegiate Guidelines Network (SIGN 2017). We will not restrict studies with respect to language, date of publication or study setting. We will search the following clinical trials registries to identify ongoing trials.

- [World Health Organization \(WHO\) International Clinical Trials Registry Platform \(ICTRP\)](#);
- [ClinicalTrials.gov](#);
- [European Union \(EU\) Clinical Trials Register](#).



## Searching other resources

We will try to identify any remaining eligible trials by searching the reference lists of all included trials, systematic reviews, meta-analyses and health technology assessment reports. We will contact experts in the area of psychological interventions and DFU, seeking information on studies relevant to the review. We will search other sources including conference proceedings, dissertation and theses databases.

## Data collection and analysis

The methodology for data collection and analysis is based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

## Selection of studies

Two reviewers (HMG and GG) will independently assess the title and abstract of all potentially relevant studies identified from the search strategy to identify those which might meet the inclusion criteria. We will retrieve the full text of studies identified as potentially relevant by at least one author. The same review authors will independently screen full text articles for inclusion or exclusion. We will resolve any disagreement by discussion or, if necessary, we will consult a third review author (CMI). All studies excluded at the full text stage will be listed as excluded studies and reasons for their exclusion will be presented in the 'Characteristics of excluded studies' table. We will report our screening and selection processes including findings at each stage in an adapted PRISMA flowchart (Liberati 2009).

## Data extraction and management

Two authors (HMG and GG) will independently extract data using a data extraction form designed specifically for this study. Any disagreements will be resolved by discussion or, if necessary, we will consult with a third review author (DD or CMI). We will extract the following information from each included study:

- trial authors
- year of publication
- country where RCT performed
- setting of care
- unit of investigation - participant, leg or ulcer
- overall sample size
- participant selection criteria
- number of participants randomised to each treatment arm
- baseline characteristics of participants per treatment arm (gender, age, baseline ulcer area, ulcer duration and previous history of ulceration)
- details of the psychological intervention including: intervention content (components, techniques, treatment materials, tailoring to individual), proposed mechanism of

action, method of delivery, number of sessions, length or time of session, background, qualifications and training of healthcare personnel delivering the intervention, target outcome

- duration of treatment
- duration of follow-up
- statistical methods used for data analysis to inform decisions on whether or not baseline adjustments have been made and if data are censored
- primary and secondary outcomes measured
- withdrawals (per treatment arm with numbers and reasons)
- source of trial funding.

We will pilot test the data extraction tool on two papers prior to the conduct of the full review and amend as necessary. One reviewer (HMG) will enter all data into Review Manager 5 (RevMan 5) software which will be checked for accuracy against the data extraction sheets by a second reviewer (GG) (Review Manager 2014). Where additional information is needed, we will try to contact authors of the original reports to provide further details.

## Assessment of risk of bias in included studies

Two reviewers (HMG and GG) will independently assess each study for risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011). This tool assesses risk of bias in sequence generation, allocation concealment, blinding, attrition, selective reporting and other topic- or design-specific issues (e.g. extreme baseline imbalance). Any disagreements regarding the risk of bias assessment will be resolved by discussion or by involving a third author (DD). The risk of bias for each study across each domain will also be summarised graphically. Criteria for judgements for each risk of bias domain are given in Appendix 2.

Risk of bias will be assessed for self-reported and objective outcome measurement for the two blinding and incomplete outcome data domains. Where information on risk of bias relates to unpublished data or correspondence with trialists, this will be noted in the 'Risk of bias' table.

## Measures of treatment effect

### *Dichotomous data*

For dichotomous data, we will present results as summary relative risks (RR) with their corresponding 95% confidence intervals (95% CI).

### *Continuous data*

For continuous data, we will use the mean difference where outcomes are measured in the same way between trials; and the standardised mean difference to combine outcomes from trials that measure the same outcome but use different scales (Higgins 2011). We will report differences with corresponding 95% CIs. Where continuous data are reported and baseline and final score are given, change score data will take precedence.



### *Time to event data*

The intervention effect for time-to-event data will be expressed as a hazard ratio. We will use the methods used to analyse time-to-event outcomes described by Tierney 2007 and detailed in Chapter 7, section 7.7.6. of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

## **Unit of analysis issues**

### *Cluster randomised trials*

If a cluster-randomised trial is included in this review, we will adjust the sample sizes for all included arms using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (where given), from a similar trial or from a trial of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC on intervention effect estimates.

We will perform a sensitivity analysis to investigate the effects of the randomisation unit, i.e. to determine the sensitivity of the effect estimates to inclusion and exclusion of cluster trials.

### *Studies with multiple arms*

For studies with multiple treatment arms, we will combine all relevant experimental intervention groups in the study (e.g. groups with psychological interventions of different duration) into a single group and all comparable relevant control intervention groups into a single control group. We will not combine control groups with different types of interventions (e.g. standard care and education on DFU healing) in a single meta-analysis and will instead analyse these separately.

### *Repeated measures*

If repeated outcome assessments are presented, we will group assessment time-frames as 12 weeks or less (short term), more than 12 weeks to six months (medium term) and more than 6 to 12 months (long term).

### *Cross-over trials*

We will incorporate outcome data from cross-over trials only at the end of the first treatment period and prior to cross-over.

## **Dealing with missing data**

We will note levels of attrition for all included trials. We will contact trial authors for missing data and if no response will consider available data.

We will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants in the group to which they were randomised, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number of people randomised minus any for whom outcomes are known to be missing. Where a randomised participant is not included in the analysis, we will

assume that there is no ulcer healing i.e., the person will contribute to the denominator only.

## **Assessment of heterogeneity**

We will assess clinical heterogeneity by exploring the variability of participants, interventions, and comparators and outcomes. In particular, we will explore the effect of gender and type of psychological approach through subgroup analyses (see ‘[Subgroup analysis and investigation of heterogeneity](#)’). Meta-analysis will only be conducted if the participants, interventions, and comparators and outcomes are sufficiently homogenous for summary estimates, including average summary estimates, to be meaningful. We will assess statistical heterogeneity in each meta-analysis using the  $I^2$  and  $\text{Chi}^2$  statistics. We will regard statistical heterogeneity as substantial/considerable if an  $I^2$  is greater than 50% or if there is a low P value (less than 0.10) in the  $\text{Chi}^2$  test for heterogeneity. Where we identify substantial clinical, methodological or statistical heterogeneity across included trials, we will use a narrative approach to data synthesis.

## **Assessment of reporting biases**

We will comprehensively search multiple databases, online trial registries and grey literature to locate all relevant publications. If there are more than 10 studies included in the meta-analysis, a funnel plot of all studies will be used to visually assess reporting biases. If we detect funnel plot asymmetry visually, we will perform exploratory analyses using the test proposed by Egger 1997 for continuous outcomes and that proposed by Harbord 2006 for dichotomous outcomes.

## **Data synthesis**

Details of included studies will be combined in a narrative review according to type of comparator, possibly by location/type of wound and then by outcomes by time period. Clinical and methodological heterogeneity will be considered and pooling undertaken when studies appear appropriately similar in terms of wound type, intervention type, duration of follow-up and outcome type.

In terms of meta-analytical approach, we are unable to pre-specify the amount of clinical, methodological and statistical heterogeneity in the included studies but it might be extensive. Thus, we anticipate using a random effects approach for meta-analysis. Conducting meta-analysis with a fixed effect model in the presence of even minor heterogeneity may provide overly narrow confidence intervals. We will only use a fixed-effect approach when clinical and methodological heterogeneity is assessed to be minimal, and the assumption that a single underlying treatment effect is being estimated holds. Chi-squared and I-squared will be used to quantify heterogeneity but will not be used to guide choice of model for meta-analysis. We will exercise caution when meta-analysed data

are at risk of small study effects because a random effects model may be unsuitable. In this case, or where there are other reasons to question the selection of a fixed effect or random effects model, we will assess the impact of the approach using sensitivity analyses to compare results from alternate models. We will report any evidence that suggests that the use of a particular model might not be robust. We may meta-analyse even when there is thought to be extensive heterogeneity. We will attempt to explore the causes behind this using meta-regression, if possible (Thompson 1999). Data will be presented using forest plots where possible. For dichotomous outcomes we will present the summary estimate as a risk ratio (RR) with 95% CI. Where continuous outcomes are measured in the same way across studies, we plan to present a pooled mean difference (MD) with 95% CI; we plan to pool standardised mean difference (SMD) estimates where studies measure the same outcome using different methods. For time-to-event data, we plan to plot (and, if appropriate, pool) estimates of hazard ratios and 95% CIs as presented in the study reports using the generic inverse variance method in RevMan 5.3. Where time to healing is analysed as a continuous measure but it is not clear if all wounds healed, use of the outcome in the study will be documented but data will not be summarised or used in any meta-analysis. Pooled estimates of treatment effect will be obtained using Cochrane RevMan software (version 5.3) (RevMan 2014).

### 'Summary of findings' tables

For each comparison, we will prepare a 'Summary of findings' table. Two reviewers will independently grade the quality of the evidence for each outcome using criteria devised by the GRADE Working Group 2004 and GRADEprofiler (GRADEpro) software (Guyatt 2008; Higgins 2011; Schünemann 2010). The four levels of evidence quality are 'high', 'moderate', 'low' or 'very low'. Quality may be downgraded due to study limitations (risk of bias), imprecision, inconsistency, indirectness or publication bias. We will include only primary outcomes in the 'Summary of findings' table, i.e. the proportion of wounds completely healed and time

to complete wound healing.

### Subgroup analysis and investigation of heterogeneity

We expect the following to introduce clinical heterogeneity and plan to carry out the following subgroup analysis to explore the impact of treatment approach.

#### 1. Male versus female participants

The rationale for the subgroup analysis between genders is because it has been suggested that there is a higher risk for ulceration and re-ulceration in men due to different psychological and social responses to chronic illness (Iverson 2008). There may be gender differences in the effects of psychological interventions in DFU. Exploring these is an important first step to developing gender-tailored programmes (Linden 2007).

#### 2. Type of psychological approach according to the classification by Goldbeck 2014. See Types of interventions section.

It is clinically important to understand which type of psychological intervention could be most successful.

We will limit subgroup analyses to primary outcomes and will explore subgroup differences by interaction tests available within RevMan 5 including the Chi<sup>2</sup> statistic and P value, and the interaction test I<sup>2</sup> value (Review Manager 2014).

### Sensitivity analysis

A sensitivity analysis will be conducted on use of a fixed versus a random effects model and on trial quality, by excluding all studies at high risk of bias in sequence generation and allocation concealment. We will limit sensitivity analyses to primary outcomes.

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\* Indicates the major publication for the study

## APPENDICES

### Appendix I. Provisional search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL)

- #1 MeSH descriptor: [Foot Ulcer] explode all trees
- #2 MeSH descriptor: [Diabetic Foot] explode all trees
- #3 (diabet\* near/3 ulcer\*):ti,ab,kw
- #4 (diabet\* near/3 (foot or feet)):ti,ab,kw
- #5 (diabet\* near/3 wound\*):ti,ab,kw
- #6 (diabet\* near/3 amputat\*):ti,ab,kw
- #7 (diabet\* near/3 defect\*):ti,ab,kw
- #8 {or #1-#7}
- #9 MeSH descriptor: [Behavior and Behavior Mechanisms] explode all trees
- #10 MeSH descriptor: [Behavioral Disciplines and Activities] explode all trees
- #11 MeSH descriptor: [Psychological Phenomena and Processes] explode all trees

#12 MeSH descriptor: [Psychology] explode all trees  
 #13 psycho\*:ti,ab,kw  
 #14 ((cognitive or interpersonal) near/4 therapy):ti,ab,kw  
 #15 ((Contract or goal) near/4 set\*):ti,ab,kw  
 #16 ((Support and (social or famil\* or friend\* or profession\*)) or counsel\* or advic\* or advis\*):ti,ab,kw  
 #17 (Motivational near/4 interview\*):ti,ab,kw  
 #18 ((chang\* or improv\* or increas\* or decreas\* or reduc\* or modif\* or activat\* or encourag\* or train\* or educat\* or teach\* or control\* or manag\*) near/4 (emotion\* or cogniti\* or behaviour\* or style or self\* or relaxation or stress or anxiety or depress\*)):ti,ab,kw  
 #19 (problem near/4 (solv\* or sort\* or control\* or manag\*)):ti,ab,kw  
 #20 coach\*:ti,ab,kw  
 #21 MeSH descriptor: [Health Education] explode all trees  
 #22 (patient and (educat\* or train\* or teach\*)):ti,ab,kw  
 #23 ((patient or health) and literacy):ti,ab,kw  
 #24 {or #9-#23}  
 #25 {and #8, #24}

## Appendix 2. The Cochrane tool for assessing risk of bias

### 1. Was the allocation sequence randomly generated?

#### Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

#### High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

#### Unclear

Insufficient information about the sequence generation process provided to permit a judgement of low or high risk of bias.

### 2. Was the treatment allocation adequately concealed?

#### Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

#### High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

## Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. This is usually the case if the method of concealment is not described, or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

### 3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

#### Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

#### High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

## Unclear

Either of the following.

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

### 4. Were incomplete outcome data adequately addressed?

#### Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on the observed effect size.
- Missing data have been imputed using appropriate methods.

#### High risk of bias

Any one of the following.

- Reason for missing outcome data are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate.



- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce a clinically relevant bias in the observed effect size.
- 'As-treated' analysis done with a substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

#### **Unclear**

Either of the following.

- Insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

### **5. Are reports of the study free of suggestion of selective outcome reporting?**

#### **Low risk of bias**

Either of the following.

- The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon)

#### **High risk of bias**

Any one of the following.

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes is/are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes was/were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review is/are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

#### **Unclear**

Insufficient information provided to permit a judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

### **6. Other sources of potential bias**

#### **Low risk of bias**

The study appears to be free of other sources of bias.

#### **High risk of bias**

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

## Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

## CONTRIBUTIONS OF AUTHORS

**Helen McGloin:** conceived the review question; developed the protocol; coordinated the protocol development; produced the first draft of the protocol; contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; approved the final version of the protocol prior to submission; and is guarantor of the protocol.

**Declan Devane:** developed the protocol; produced the first draft of the protocol; contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

**Caroline McIntosh:** developed the protocol; produced the first draft of the protocol; contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

**Kirsty Winkley:** contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

**Georgina Gethin:** conceived the review question; developed the protocol; coordinated the protocol development; produced the first draft of the protocol; contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

## Contributions of the editorial base

Anne-Marie Glenny (Editor): edited the protocol; advised on methodology and protocol content; approved the final protocol prior to submission.

Gill Rizzello (Managing Editor): coordinated the editorial process; advised on content; edited the protocol.

Reetu Child and Naomi Shaw (Information Specialists): designed the search strategy and edited the search methods section.

Zipporah Iheozor-Ejiofor (Methodologist): advised on methodology.

Ursula Gonthier (Editorial Assistant): edited the reference section.

## DECLARATIONS OF INTEREST

Helen McGloin: none known.

Declan Devane: none known.

Caroline McIntosh: none known.

Kirsty Winkley: I am co-applicant on a NIHR Programme Development grant to reduce the impact of diabetic foot ulceration.

Georgina Gethin: I have received honoraria for presenting at industry sponsored meetings in topics unrelated to this review.

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